News and Resources from the National Institutes of Health

Urologic Diseases
Research Updates

National Kidney and Urologic Diseases Information Clearinghouse Winter 2009

NIDDK Hosts Prostate Workshop

Prostate problems, though long considered an inevitable part of aging for men, may be preventable, according to scientists who participated in a workshop sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

The workshop's goals were to review the state of the science around benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS), identify data gaps, and prioritize future research. Central to the workshop was identifying modifiable risk factors—those factors that can be controlled or changed, such as diet and smoking.

BPH is an enlargement of the prostate—a gland below the bladder that surrounds the urethra—a common condition affecting about 50 percent of men in their 50s. When enlarged, the prostate can restrict urine flow from the bladder.

LUTS are the symptoms thought to be related to BPH; however, LUTS are not exclusive to BPH or men. LUTS in men include frequent urination, difficulty starting or maintaining a urine stream, the inability to completely empty the bladder, the need to get up at night to urinate, dribbling, and the tendency to retain urine in the bladder. Between 26 and 46 percent of men ages 40 to 79 have moderate to severe LUTS.

"Can we stop the progression of BPH/LUTS? Or, even more importantly, can we prevent the disease?" Robert A. Star, M.D., director of the NIDDK's Division of Kidney, Urologic, and Hematologic Diseases asked the assembled group of epidemiologists, basic scientists, and urologists.

Defining BPH/LUTS

Key to identifying modifiable risk factors is defining the problem, but according to John Wei, M.D., M.S., associate professor of urology at the University of Michigan, "there are as many definitions of LUTS as there are clinical trials," making comparisons between studies difficult.

A universal definition of LUTS is lacking because men can develop LUTS from a variety of causes related or unrelated to the prostate. And while some men have severe LUTS and relatively minor BPH, others have significant prostate enlargement but are not bothered by symptoms. These observations suggest the existence of multiple LUTS subtypes with diverse etiologies and corresponding risk factors.

Prostate Workshop, continued on page 2

Inside This Issue

NIDDK
National Institute of Diabetes and Digestive and Kidney Diseases

PROSTATE WORKSHOP, from page 1

Biomarkers and Endpoints

"Seventy-five percent of our questions can be answered by existing cohorts."

Steven Jacobsen, M.D., Ph.D.
Director of Research, Southern California Kaiser Permanente Medical Group

Surrogate biomarkers and measurable endpoints are needed to characterize LUTS subtypes, according to Elizabeth Platz, Sc.D., M.P.H., associate professor of epidemiology at the Johns Hopkins University Bloomberg School of Public Health.

Prostate volume, although widely used in clinical research, has fallen out of favor as a surrogate biomarker for LUTS. "Prostate volume simply establishes a man has a prostate," said Wei, suggesting size has only limited bearing on symptoms or disease progression.

Self-reported measures, such as the International Prostate Symptom Score—essentially a patient's rating of symptom severity and quality of life—would provide excellent and inexpensive surrogate biomarkers and endpoints for LUTS cohort studies, according to Alan R. Kristal, Dr.P.H., of the Fred Hutchinson Cancer Research Center.

Several promising serum biomarkers were recognized at the workshop, including the protein JM-27, which was shown by the NIDDK-funded Prostatic Samples Analysis (MPSA) Consortium to be higher in men with symptomatic BPH than in men with asymptomatic BPH. MPSA is an outgrowth of the Medical Therapy of Prostatic Symptoms clinical trial, which was originally designed to test the effectiveness of the drugs finasteride and doxazosin at stopping or slowing the progression of BPH.

PROSTATE WORKSHOP,
continued on page 5

Likely Modifiable Risk Factors

Participants at the National Institute of Diabetes and Digestive and Kidney Diseases Workshop on Modifiable Risk Factors for Lower Urinary Tract Symptoms (LUTS)/Benign Prostatic Hyperplasia (BPH) constructed a list of modifiable factors that likely increase or decrease risk for BPH/LUTS, including

- physical activity level
- obesity or waist circumference
- diet
- alcohol consumption
- diabetes
- smoking

Participants tagged potential modifiable risk factors worth exploring, including

- hypercholesterolemia
- hypertension
- depression
- stress
- use of medications, including nonsteroidal anti-inflammatory drugs and statins

Urologic Diseases
Research Updates

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Urologic Diseases Research Updates, an email newsletter, is sent to subscribers by the National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC). The newsletter features news about urologic diseases, special events, patient and professional meetings, and new publications available from the NKUDIC and other organizations.

If you would like to subscribe, go to *http://catalog.niddk.nih.gov/newsletter.cfm*. You can read or download a PDF version of the newsletter at *www.kidney.niddk.nih.gov/about/newsletter.htm*.

Executive Editor: Leroy M. Nyberg Jr., M.D., Ph.D.

Dr. Nyberg is the director of urology and urology centers programs at the National Institute of Diabetes and Digestive and Kidney Diseases, part of the National Institutes of Health (NIH) in Bethesda, MD. Dr. Nyberg is a graduate of Tufts University in Boston, Columbia University in New York, and the University of Massachusetts Medical School in Worcester and completed residency training in urology at The Johns Hopkins Hospital in Baltimore. He has also held faculty positions in urology at The Johns Hopkins Medical School, in urology and biochemistry at the Medical University of South Carolina, and in urology at the University of Connecticut. Dr. Nyberg received the Distinguished Service Award from the American Urological Association for significant clinical and research contributions to urology. He also received the NIH Directors Award for excellence for the development of urologic research programs at the NIH.

Pelvic Floor Disorders Affect Almost a Quarter of U.S. Women

Nearly 25 percent of U.S. women are affected by pelvic floor disorders, according to a study funded by the National Institutes of Health.

"Pelvic floor disorders affect a substantial proportion of women and increase with age."

Ingrid Nygaard, M.D.
Professor, Department of Obstetrics and Gynecology, University of Utah School of Medicine

The Pelvic Floor Disorders Network (PFDN)—a collaboration of U.S. health care providers and researchers working to improve the care and daily lives of women with pelvic floor disorders—submitted questions about pelvic floor disorders for inclusion in the 2005–2006 National Health and Nutrition Examination Survey (NHANES). NHANES is a periodic survey of the U.S. population conducted by the Centers for Disease Control and Prevention's National Center for Health Statistics.

Almost 2,000 women—all 20 or older and not pregnant—answered questions about symptoms of pelvic floor disorders and underwent standardized physical examinations. The results, reported in the September 17, 2008, *Journal of the American Medical Association,* are the first to document the extent of pelvic floor disorders in a nationally representative sample.

The study was supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the Office of Research on Women's Health, with additional funding from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

The three main pelvic floor disorders are urinary incontinence (UI), fecal incontinence, and pelvic organ prolapse (POP). Pelvic floor disorders arise when the muscles and ligaments that form a sling across a woman's pelvic opening weaken or are injured. In POP, organs such as the uterus, bladder, and bowel collapse onto the vagina and cause a bulge through the vaginal canal, which

can cause discomfort. All three disorders can make physical activity difficult and interfere with sexual function.

Age, Weight, and Childbirth

Overall, about 24 percent of women reported moderate to severe symptoms of at least one pelvic floor disorder, according to the study. About 16 percent experienced UI, 9 percent experienced fecal incontinence, and 3 percent experienced POP.

"Pelvic floor disorders affect a substantial proportion of women and increase with age," said lead study author Ingrid Nygaard, M.D., professor of urogynecology at the University of Utah School of Medicine.

According to the study, pelvic floor disorders affect about 10 percent of women ages 20 to 39, 27 percent of women ages 40 to 59, 37 percent of women ages 60 to 79, and nearly half of women age 80 or older.

Weight plays a role, too. Pelvic floor disorders affect 15 percent of underweight women, 26 percent of normal-weight women, and 30 percent of overweight and obese women, according to the study.

Pelvic Floor Disorders,
continued on page 5

Alfuzosin Fails to Reduce Prostatitis Symptoms

The commonly prescribed drug alfuzosin failed to significantly reduce chronic prostatitis symptoms in men who participated in a 12-week clinical trial sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The results were reported December 18, 2008, in the *New England Journal of Medicine*.

"We have conclusively shown that a drug commonly prescribed for men with chronic prostatitis did not significantly reduce symptoms compared with a placebo."

Griffin P. Rodgers, M.D., M.A.C.P.
Director, NIDDK

"Although these results are disappointing, it is just as important to find out what doesn't work as it is to know what does," said NIDDK Director Griffin P. Rodgers, M.D., M.A.C.P. "We have conclusively shown that a drug commonly prescribed for men with chronic prostatitis did not significantly reduce symptoms compared with a placebo."

Alfuzosin is an alpha blocker, a class of drugs that relaxes the smooth muscle of the bladder and prostate.

A Common Problem

Chronic prostatitis, which has no known cause and no uniformly effective therapy, is the most common type of prostatitis seen by physicians. Men with this condition experience pain in the genital and urinary tract areas, lower urinary tract symptoms such as pain in the bladder area and during urination, and sexual problems that can severely affect their quality of life. Population-based surveys estimate that 6 to 12 percent of men have prostatitis-like symptoms.

A total of 272 men diagnosed with chronic prostatitis were randomly assigned to take either alfuzosin or an identical-looking placebo. Of these, 233 men completed the trial. The primary outcome was a decrease, or improvement, in the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) of at least four points over 12 weeks of treatment.

A four-point decrease in the NIH-CPSI score has been shown to be the minimal clinically significant difference perceived by patients as beneficial. The index measures the three most important symptoms of chronic prostatitis—pain, urination problems, and negative effects on quality of life.

Although 49.4 percent of men in both groups experienced a four-point or greater score reduction, the alfuzosin group showed no improvement over the placebo group. "A 12-week course of alfuzosin as compared with placebo did not result in a clinically meaningful reduction in symptoms, as measured by the NIH-CPSI," said lead study author J. Curtis Nickel, M.D., professor of urology at Queen's University in Kingston, Ontario, Canada.

Lack of Evidence

Despite a lack of rigorous evidence supporting the use of antibiotics or alpha blockers for chronic prostatitis, more than 75 percent of primary care physicians often prescribe antibiotics and more than 50 percent regularly prescribe alpha blockers such as alfuzosin for the condition, according to a recent NIDDK-supported survey.

Previous studies of alpha blockers conflict. Whereas several smaller trials showed alpha blockers improved prostatitis symptoms, a larger

Alfuzosin,
continued on page 5

Prostate Workshop, from page 2

Future Studies

During facilitated discussions, workshop participants identified knowledge gaps and devised future studies. Most agreed that leveraging existing clinical studies would be the most economic and fastest way to characterize LUTS subtypes.

"Seventy-five percent of our questions can be answered by existing cohorts," surmised Steven Jacobsen, M.D., Ph.D., director of research at the Southern California Kaiser Permanente Medical Group. Such an approach would rely on data and specimens from other studies, related or unrelated to BPH/LUTS, or "piggybacking" with ongoing or new studies.

Smaller proof-of-concept studies would complement larger epidemiological studies, Platz suggested, which would test specific interventions such as a case-control trial evaluating the effect of diet and exercise on slowing LUTS progression.

A formal list of recommendations for studying modifiable risk factors for BPH/LUTS is forthcoming.

Publications about prostate problems are available from the National Kidney and Urologic Diseases Information Clearinghouse at *www.kidney.niddk.nih.gov/kudiseases/a-z.asp.* ■

Pelvic Floor Disorders, from page 3

Pelvic floor disorders also correlate with the number of times a woman has given birth. Prevalences of UI and POP were twice as high among women who had twice given birth vaginally compared with women who had never given birth vaginally, according to the study.

"The study results underscore the need to identify the causes of pelvic floor disorders and the means to prevent and treat them," said NICHD Director Duane Alexander, M.D.

The NIDDK Information Clearinghouse has free publications about pelvic floor disorders at *www.kidney.niddk.nih.gov/kudiseases/a-z.asp#p.* For information about the PFDN, go to *www.nichd.nih.gov/health/topics/Pelvic_Floor_Disorders.cfm.* ■

Alfuzosin, from page 4

study that included men with long-standing symptoms and previous alpha blocker use showed no improvement. The current study tested whether alpha blockers might be more beneficial to men with recently diagnosed prostatitis and therefore was limited to men who had symptoms for 2 years or less and had never before taken alpha blockers.

"Our findings do not support the use of alpha blockers for treating new cases of chronic prostatitis," said Nickel. "But the results of our study will inform future clinical trials of alpha blockers and other potential therapies."

More information about the Trial to Compare Alfuzosin Versus Placebo in the Treatment of Chronic Prostatitis/Chronic Pelvic Pain Syndrome can be found at *www.ClinicalTrials.gov.*

Publications about prostate problems are available from the National Kidney and Urologic Diseases Information Clearinghouse at *www.kidney.niddk.nih.gov/kudiseases/a-z.asp.* ■

NIDDK Hosts Urinary Incontinence Symposium

Researchers met in Bethesda, MD, January 7–9, 2009, to explore new directions in understanding and treating urinary incontinence (UI). Through lectures, poster presentations, and discussions, UI experts from around the globe exchanged information and ideas about a condition that for many people is too embarrassing to talk about.

"The complexity of urinary incontinence requires collaborative approaches that involve researchers from many fields."

Griffin P. Rodgers, M.D., M.A.C.P.
Director, NIDDK

"The complexity of urinary incontinence requires collaborative approaches that involve researchers from many fields," said National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Director Griffin P. Rodgers, M.D., M.A.C.P. "The NIDDK is committed to supporting promising new approaches to the treatment of this disease."

Fostering collaboration is precisely what two National Institutes of Health initiatives—the Urinary Incontinence Treatment Network (UITN) and the Pelvic Floor Disorders Network (PFDN)—are accomplishing. Prior to these initiatives, investigators defined treatment outcomes many different ways, according to Ann Gormley, M.D., professor of surgery, Dartmouth Medical School's urology section. Doing so confounded study comparisons. Since then, "the UITN and PFDN have established standardized definitions and benchmarks that can be used to measure progress in future studies," Gormley said.

The UITN is funded by the NIDDK; the PFDN is funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development.

UI, or the inability to retain urine, is common in older people but can be a problem at any age. The annual cost of managing and treating UI in the United States has been estimated to be as high as $32 billion, according to Ananias Diokno, M.D., F.A.C.S., executive vice president and chief medical officer of the William Beaumont Hospital at Royal Oak, MI.

New Directions

With a focus on topics having potentially broad clinical utility, participants at the NIDDK New Directions in Urinary Incontinence Symposium identified major research needs and opportunities, including

- clinical trials that include more diverse populations
- better predictors of treatment outcomes and measures of treatment success
- individually tailored therapies
- techniques to minimize treatment complications
- promotion of behavioral therapies
- greater collaboration with colleagues in fecal incontinence research, nursing, and geriatrics
- better synthetic meshes for the surgical treatment of UI
- increased understanding of urethral function
- exploration of genetic contributors to UI

A detailed summary of recommendations from the symposium will be presented to the NIDDK Council, an appointed board representing the scientific and lay communities that help guide the NIDDK's research portfolio.

The NIDDK has fact sheets and easy-to-read booklets about UI at *www.kidney.niddk.nih.gov/kudiseases/a-z.asp#u.* ■

Zerhouni Ends Tenure as NIH Director

Deputy Director Kington Steps in as Acting Director

Elias A. Zerhouni, M.D., a physician-scientist and world-renowned leader in radiology research, ended his tenure as director of the National Institutes of Health (NIH). From May 2002 through October 2008, Zerhouni led the agency through a challenging period that required innovative solutions to transform basic and clinical research into tangible benefits for patients and their families.

"I have had the privilege of leading one of the greatest institutions in the world for six-and-a-half years."

Elias A. Zerhouni, M.D.

Zerhouni plans to pursue writing projects and explore other professional opportunities.

"I have had the privilege of leading one of the greatest institutions in the world for six-and-a-half years," Zerhouni said. "NIH's strength comes from the extraordinary commitment and excellence of its people in serving a noble mission. It also comes from the nation's scientific community, whose discoveries alleviate the suffering of patients throughout the world."

NIH Roadmap

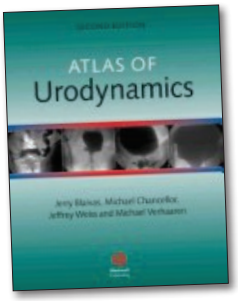
The hallmark of Zerhouni's tenure is the NIH Roadmap for Medical Research, launched in 2003 after extensive consultations with the scientific community. The NIH Roadmap brought together the NIH's 27 Institutes and Centers to fund compelling research initiatives that could have a major impact on science but that no single Institute could tackle alone.

Reaching out to the Public

Under Zerhouni's leadership, the NIH reached out to the public in an unprecedented way with the communication of science-based health information and scientific results. He led efforts to make the incomparable resources of the NIH and its grantees accessible to the public. Key to these efforts are the health education programs across the agency, including the development of materials for people who have literacy, language, or access barriers.

The NIH is part of the U.S. Department of Health and Human Services and is the nation's premiere biomedical research agency. The agency has more than 18,000 employees and a fiscal year 2008 budget of $29.5 billion. It supports more than 325,000 research personnel at more than 3,100 institutions throughout the United States and around the world.

Raynard S. Kington, M.D., Ph.D., NIH deputy director under Zerhouni, will serve as acting director until a permanent director is appointed by President Obama. ■



Featured in the NIDDK Reference Collection

"Genital Prolapse"

This chapter about pelvic organ prolapse (POP) is from the *Atlas of Urodynamics,* which provides a comprehensive, detailed look at the indications, technology, and use of urodynamics in modern urologic practice. The purpose of urodynamic testing is to measure and record various physiological variables while the patient is experiencing those symptoms that make up the presenting complaint. POP is defined as the abnormal descent of the pelvic organs into the vagina. Women with POP may present with a plethora of lower urinary tract symptoms, including urinary frequency, urgency, hesitancy, incomplete emptying, and incontinence. The chapter includes a brief text section and presents case illustrations accompanied by figures and black-and-white photographs of actual urodynamic tests. The authors discuss the effect of POP on urination and the recommended urodynamic evaluation approach. The *Atlas of Urodynamics* is available from Blackwell Publishing, Inc., P.O. Box 20, Williston, VT 05495, 1–800–216–2522, *orders@aidcvt.com, www.blackwellpublishing.com.*

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Reference Collection is a free, online database that helps health care professionals, health educators, patients, and the general public find educational materials not typically referenced in most databases. The NIDDK does not control or endorse the information contained in this collection; the information is provided as a convenience to our visitors. To find more resources about urologic diseases, visit *www.catalog.niddk.nih.gov/resources.* ■

Additional Resources

Urinary Incontinence in Women

Millions of women experience involuntary loss of urine, called urinary incontinence (UI). Some women may lose a few drops of urine while running or coughing. Others may feel a strong, sudden urge to urinate just before losing a large amount of urine. Many women experience both symptoms. UI can be slightly bothersome, emotionally distressful, or totally debilitating.

Urinary Incontinence in Women, a fact sheet from the National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC), explains the various types of UI, including urge incontinence, stress incontinence, overactive bladder, functional incontinence, and others. The fact sheet, which includes diagrams of the bladder and the pelvic muscles that control urine, describes the causes, evaluation, and treatment of UI in women. The fact sheet is available from the NKUDIC website at *www.kidney.niddk.nih.gov/kudiseases/pubs/uiwomen.*

Urinary Incontinence in Men

Men can develop UI, or the accidental leakage of urine, from a variety of causes, including nerve damage due to illness or injury, inflammation of the prostate, or an overactive bladder. UI is more common in older men but is not an inevitable part of aging.

Urinary Incontinence in Men, a fact sheet from the NKUDIC, explains what causes UI in men, describes signs and symptoms, and summarizes available treatments. The fact sheet is available from the NKUDIC website at *www.kidney.niddk.nih.gov/kudiseases/pubs/uimen.*

Additional Resources,
continued on page 9

Additional Resources, from page 8

New Interactive Tools

New to the Interactive Health Education Tools section of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) website are

Streaming Audio

- Almost a Quarter of U.S. Women Are Affected by Pelvic Floor Disorders
- NIDDK Launches Effort to Advance Study of Urologic Chronic Pelvic Pain Disorders

The NIDDK interactive tools section consolidates tools and resources about urologic diseases from the National Institutes of Health (NIH) and the National Library of Medicine. To access these resources, visit *www2.niddk.nih.gov/HealthEducation/InteractiveTools.*

Featured Website

Children and Clinical Studies

A new website developed by the NIH informs parents and health care providers about clinical studies for children. Featuring video interviews with researchers, parents, and children involved in clinical trials, the website addresses why research on children is important, factors to consider when deciding whether to enroll in a clinical trial, and the challenges and benefits of participating. To visit the site, go to *www.childrenandclinicalstudies.nhlbi.nih.gov.*

Upcoming Meetings, Workshops, and Conferences

The National Institute of Diabetes and Digestive and Kidney Diseases Information Clearinghouses will be exhibiting at the following upcoming events:

American College of Physicians Internal Medicine

April 23–25 in Philadelphia.
For more information, go to *www.acponline.org/meetings/internal_medicine/2009/attendees/?pr13r.*

American Urological Association Annual Meeting

April 25–30 in Chicago.
For more information, go to *www.aua2009.org.*

American Nephrology Nurses Association 40th National Symposium

April 26–29 in San Diego.
For more information, go to *www.annanurse.org.*

American Academy of Physician Assistants 37th Annual Conference

May 23–28 in San Diego.
For more information, go to *www.aapa.org/annual-conf/sandiego09/index.php.*

American Academy of Nurse Practitioners 24th National Conference

June 17–21 in Nashville, TN.
For more information, go to *www.aanp.org/AANPCMS2/Conferences.*

NIH Publication No. 09–5743
March 2009